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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,934	KORENBERG ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,15-17,19-31 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-17,19-31 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A (sequence alignment)*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group 1, with species election megakaryocytic abnormality in the reply filed on 07 June 2004 is acknowledged. The traversal is on the ground(s) that the various splicing variants disclosed in the instant application share common technical feature, which they all belong to the SH3D1A gene. This argument is not persuasive for the reasons set forth in the Office action mailed on 04/06/2004.

As the International Search Report (ISR) indicated, each of the isolated nucleic acid encoding each of the five different splicing variants from SH3D1A gene is drawn to a different general inventive concept because each of the nucleic acid encodes a different splicing variant that has a different biological function. Note the ISR.

Second, a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; (2) A product and a process of use of said product; (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; (4) A process and an apparatus or means specifically designed for carrying out said process; or (5) A product, and a process specially adapted for the manufacture of said product, and an

apparatus or means specifically designed for carrying out said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d).

Claims 1, 2, 5-12, 17, 20, 21, 24, 26-31, and amended, and claim 58 is new. The amended claims are drawn to nucleic acid encoding the first splicing variant. Claims 1-12, 15-17, 19-31, and 58 are pending and are examined on merits.

All of the documents cited in the ISR have been considered.

Sequence Rules

This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. Therefore, the disclosure of the specification is objected because a sequence identifier is not associated with each of the nucleotides and amino acids sequences shown at Figures 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, and 18, which are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

37 CFR 1.821(d) reads:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by SEQ ID NO:" in the text of the description or claims, even if the sequence is embedded in the text of the description or claims of the patent application.

37 CFR 1.821(a) presents a definition for "nucleotide and/or amino acid sequences." The instant application contains an unbranched specifically defined

sequence of more than ten nucleotides, and more than four amino acid sequences at Figures 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, and 18. The copy of "Sequence Listing" filed on 10/03/2001 has numerous sequence identifiers. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings in Patent Applications (1998), including Tables 1 through 6 in Appendix 2 (see MPEP § 2422).

This objection would be obviated by adding the corresponding SEQ ID NO to each of the nucleotides and amino acids sequences shown at Figures 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, and 18 in "BRIEF DESCRIPTION OF THE DRAWINGS" beginning page 8.

Claim Objections

Claims 4, and 6-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the

claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 4 depends on claim 2 whose scope is limited to single species i.e. SEQ ID NO:1, which appears to cDNA according to pages 56-57 of the specification. However, the scope of claims 4, 6-12 broadens the scope of claim 2 because the scope of claims 4, and 6-12 is not limited to SEQ ID NO:1. Amending claim 4 to depend on claim 1 would obviate this objection.

For the purpose of a compact prosecution, the Office will treat claims 4, and 6-12 depend on the base claim 1. However, this treatment does not relieve applicant the burden of responding to this objection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17, and 22 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 17, and 22, as written, do not sufficiently distinguish over nucleic acids, proteins, cells and antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g.,

by insertion of "Isolated" or "Purified" as taught by the original claim 1 of specification. See MPEP 2105.

Claims 1-12, 15-17, 19-31, and 58 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Claims 1-12, 15-17, 19-31, and 58 are interpreted as drawn to SEQ ID NO:1 (a cDNA from human SH3D1A gene on human chromosome 21), which encodes SEQ ID NO:2.

This utility rejection is made because neither the specification nor any art of record teaches what the biological activities of SH3D1A gene product are. In fact, Guipponi et al., (11/01/1998, Genomics, vol. 53, pages 369-376), a publication after the effective filing date (04/16/1998) of the instantly claimed invention, teach at the last paragraph of page 375 that neither the physiological function of ITSN (note this is alias for SHD1A gene product) nor any disorder associated with a malfunction of the gene product (note the abstract) is known in the art.

Although the specification speculates the possible function of the SH3DIA gene product in involvement of "developmental and/or cell regulatory phenomena", "protein and protein interactions", and "maintenance of the cytoskeleton" based on sequence homology, the art generally acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

Scott et al (Nature Genetics, 1999, 21:440-443) teach that the function of newly identified gene products is unpredictable even when the database searches reveal significant homology to proteins of known function. Scott et al teaches that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. states that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-

250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of the newly identified instantly claimed protein.

The specification asserts that the claimed invention could be used for detection of megakaryocytic abnormality. The specification especially at page 53

lines 14-28 suggests that SH3DIA gene might contributes to the development of familial platelet disorder. However, this assertion based on detection of over-expression of SH3DIA mRNA in a single person afflicted with familial platelet disorder is not substantial enough in light of the post-filing publication by Song et al., (October 1999, Nature Genetics, vol. 23, pages 166-175) et al. Song et al., unequivocally teach that a mutation in a nearby gene on human chromosome 21 i.e. CBFA2 causes familial platelet disorder.

The specification does not establish involvement of the claimed invention in the etiology of any specific disease. None of the disorders listed at page 6 lines 5-10 is caused by the different distribution of SH3DIA mRNA. The SH3DIA mRNA tissue distribution (at page 58 and Fig. 17) does not lead to diagnose any of the disorders, although the specification speculates a possible involvement of the SH3DIA in development of leukemia and neural abnormalities and dysfunction. None of the disorders listed at page 6, lines 5-10 of the specification is caused by the malfunction of the claimed gene product. The specification does not have any substantial use for the antibody or the protein either because the biological activity of the gene product is not disclosed in the specification. The asserted uses of the claimed invention as hybridization probes, and antisense do not lead to substantial uses of the claimed invention due to unknown functions of the claimed nucleic acid and/or the protein encoded by the claimed invention. The specification does not have any substantial use for pharmaceutical compositions, diagnostic assay, and methods of treatment

because the specification does not teach what disease(s) is caused by a malfunction of the claimed invention or the protein encoded by it.

Further research is required to use the instantly claimed invention for the asserted diagnostic and therapeutic applications. After further research, a specific and substantial utility might be found for the claimed invention. The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claims 1-12, 15-17, 19-31, and 58 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the EH domains and SH3 domains" in line 3. There is insufficient antecedent basis for this limitation in the claim. Amending the claim to depend on claim 5 instead of claim 4 could obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-12, 15-17, 19-31, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made because claims 1, 3-12, 15-17, 19-31, and 58 are interpreted as drawn to genus of nucleic acid molecules encoding a genus of polypeptides "**comprising**" "**a fragment**" (note the claim limitation in line 2 of claim 1) of SEQ ID NO:2, or genus of vectors comprising said nucleic acid molecules, host cells comprising said vectors, method of producing polypeptides using said host cells.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the only factor in claims 1, 3, 15, 16, 2, 23-31 is nucleic acid encoding a polypeptide comprising a "fragment". The claims do not identify a function associated with the genus that minimally contains an unspecified length of "a fragment". Although claim 4 depends on claim 2 that is not rejected under written description, claim 4 is rejected under written description because the scope of claim 4 does not appear to be limited to SEQ ID NO:1 (note claim objection above). Further, claim 4 recites "genomic DNA". Guipponi et al., (01 November 1998, Genomics, vol. 53, pages 369-376) teach at page 370 that a genomic DNA includes "introns" among other DNA elements. The specification does not describe how the introns of the gene encoding SEQ ID NO:2 look like.

As for claims 5-12, they recite specific fragments of SEQ ID NO:2 but the claims do not specify what kind(s) of function is associated with the claimed

genus comprising the various recited fragments. As for claims 17, 19, and 20 reciting "oligonucleotide" in the preamble, this written description rejection is based on the Office's interpretation of the scope encompassed by the claims 17, 19, and 20 not only includes primers for PCR but also could include a full-length cDNA.

The specification at page 15 reads:

> Oligonucleotides which are complementary may be obtained as follows: The polymerase chain reaction is then carried out using the two primers. See PCR Protocols: W Guide to Methods and Applications (742. Following PCR amplification, the PCR-amplified regions of a viral DNA can be tested for their ability to hybridize to the three specific nucleic acid probes listed above. Alternatively, hybridization of a viral DNA to the above nucleic acid probes can be performed by a Southern blot procedure without viral DNA amplification and under stringent hybridization conditions as described herein.

The broadest reasonable interpretation of the claimed oligonucleotide thus includes PCR amplified products. Guipponi et al., (1998, Genomics, vol. 53, pages 369-376) teach that a long piece of nucleic acid such as cDNA encoding a full-length ORF could be amplified by PCR. Thus, the Office concludes that scope of the claims 17, 19, 20 includes not only primers with "at least 15 nucleotides" for PCR but also includes PCR products, which could include allelic variants or other isoforms, or homologs that could obtained result of PCR-amplification.

As for claim 22 reciting "antisense molecule", the Office again turns to the specification for guidance in terms of the scope encompassed by the preamble since claim 22 does not have any explicit structure of genus of the claimed products.

The specification at page 19 reads:

> Antisense nucleotides or polynucleotide sequences are useful in preventing or diminishing the expression of the SH3DIA gene, as will be appreciated by those skilled in the art. For example, polynucleotide vectors containing all or a portion of the SH3DIA gene or other sequences from the SH3DIA region (particularly those flanking the SH3DIA gene) may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with SH3DIA transcription and/or translation and/or replication.

Based on the disclosure above, antisense is broadly interpreted as a genus of nucleic acid molecules of claim 1, comprising all or a portion of the SH3DIA gene or other sequences from the SH3DIA region ("particularly those flanking the SH3DIA gene"), which the instant specification does not have written description for.

The present claims encompass full-length genes from homologs and allelic variants that are not further described. There is substantial variability among the species of nucleic acid molecules encompassed within the scope of the claims because the claims recite "a fragment" of a full-length protein. They are structurally unrelated. A description of a genus may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Since SEQ ID NO:1 is a human cDNA, and the scope encompasses other cDNA such as human allelic variants, and homologs from dogs, etc., the breath of the claims as reading on genes yet to be discovered, the lack of correlation between the structure and the function of the genes, it is concluded that the written description requirement is not satisfied.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid molecules, given that the specification has only described nucleic acid encoding SEQ ID NO:2 protein. Therefore, only isolated nucleic acid comprising SEQ ID NO:1, nucleic acid encoding SEQ ID NO:2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 15-17, 19-31, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue"

include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the claimed invention is interpreted as drawn to SEQ ID NO:1 (a cDNA from SH3D1A gene) isolated from human chromosome 21 for use in detection of megakaryocytic abnormality.

The specification at page 53 lines 14-27 and Fig. 3 discloses that the SH3DIA is mapped to chromosome 21, and mRNA analysis obtained from an individual with familial platelet disorder (FPD) shows a significantly higher expression of SH3D1A.

However, one of skilled in the art would have a reason to doubt familial platelet disorder (FPD) or any other megakaryocytic abnormality could be detected by the claimed nucleic acids because the post-filing date publication, Song et al., (October 1999, Nature Genetics, vol. 23, pages 166-175) unequivocally teach at the abstract that that FPD is caused by mutations in CDFA2 gene, not SH3D1A.

Further, OMIM (Online Mendelian Inheritance in Men) with the update history of 2002 with the accession number #601399 downloaded on 7/28/04 from url>>ncbi.nlm.nih.gov also teaches that the art recognizes mutation in CDFA2

gene, not SH3D1A gene is associated with FPD megakaryocytic abnormality phenotype.

Next, claims 27-29 are broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Thus, claims 27-29 encompass host cells that have been transfected with the vector of claim 23 that is comprised within a transgenic animal, including human or nonhuman animals treated using gene therapy.

The specification at page 7 lines 15-24 discloses supplying "all or portion of the SHD1A gene placed in appropriate vectors or delivered to target cells in more direct ways such that the function of the SH3D1A protein is reconstituted." The teachings of the specification cannot be extrapolated to the enablement of the claimed invention, broadly interpreted as drawn to include gene therapy because the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to have a reasonable expectation of success in making and using the claimed invention without the need to perform additional, and an undue amount of experimentation.

The specification does not teach any method of overcoming technical difficulties the art has been facing with the gene therapy. For example, Friedmann (Scientific American, June 1997, pages 96-101), Verma and Somia (1997, Nature, vol. 389, pages 239-242), and Rubanyi (2001, Molecular Aspects of Medicine 22, pages 113-142) all teach that gene therapy art still faces major hurdle to overcome. Rubanyi at the abstract teaches that the prerequisite of successful gene therapy includes "therapeutically suitable genes with a proven

role in pathophysiology of the disease". The instant specification fails at this first prerequisite because the specification does not teach a proven role in a pathophysiology of SHD1A. In other words, the specification fails to teach which disease would benefit from gene therapy using the instant claimed invention. Further, Verma and Somia teach the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Friedman summaries the current state of gene therapy as "treating disease by providing needed gene remains a compelling idea, but clinical and basic researchers still have much to do before gene therapy can live up to its promise" (note the italicized headline at the top of page 96). Amending claims 27-29 to recite "isolated" before "host cell" would obviate this part of rejection.

Claim 22 recites "antisense". The specification at page 19 discloses an antisence is used to prevent or diminishing the expression of the SH3D1A gene. However, the specification does not teach which disease would benefit preventing or diminishing expression of the SH3D1A gene. As stated above, Song et al., unequivocally teach that mutation in CBFA2 causes familial platelet disorder, not SH3D1A.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to make nucleic acid capable of detecting megakaryocytic abnormality, and how to use the claimed invention, and broad breath of the claims, it is concluded that undue experimentation is required to practice the full scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 6, 9-12, 15-17, 19-31, and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/31625 (10 Oct. 1996).

The claims 1, 3, 4, 6, 9-12, 15-17, 19-31, and 58 are interpreted as drawn to an isolated nucleic acid encoding an undefined length of fragment of SEQ ID NO:2 protein (claims **1, 58**), or said nucleic acid being DNA (claim **3**), being cDNA (claim **4**, based on the interpretation of claim 4 depending on claim 1, see claims objection for further details on this matter), said nucleic acid encoding an amino acid sequence comprising one or more myristoylation sites in any of the EH and SH3 domains (claim **6**), encoding an amino acid sequence comprising residue 740-800 of SEQ ID NO:2 (claim **9**), 908 to 966 of SEQ ID NO:9 (claim **10**), 999 to 1062 of SEQ ID NO:2 (claim **11**), 1080 to 1138 of SEQ ID NO:2 (claim **12**), a detectable marker is attached to the nucleic acid of claim 1 (claim **15**), said detectable marker is radioactive isotope or other art-known label (claim **16**), oligonucleotide with the minimum length of 15 nucleotide capable of specifically hybridizing with the nucleic acid of claim 1 (claim **17**), said oligonucleotide is labeled with the various art-known detectable marker (claims **19**, and **20**), complementary to nucleic acid of claim 1 (claim **21**), antisense

(claim **22**), and vector for protein expression in an art-known expression system (claims **23-26**), host cells (claim **27-29**), method of producing and obtaining a protein encoded by the vector (claim **30**, and **31**).

WO 96/31625 teaches an isolated DNA, more specifically cDNA encoding an amino acid sequence comprising residue 684-1143 of the instant SEQ ID NO:2 (note the attached Exhibit A, total 2 pages of sequence alignment of instant SEQ ID NO:2 against cDNA encoding the human SH3P17 gene product with ID AAT39795 from the WIPO sequence database i.e. Geneseq). Since the instant specification at Fig. 2 discloses that residues 684-1143 of instant SEQ ID NO:2 encompass all of SH3 domains i.e. SH3 1-4, and those SH3 domains have multiple myristoylation sites, the cDNA encoding residues 684-1143 of SEQ ID NO:2 also meets the limitation of claim 6.

WO 96/31625 teaches expression vectors, and the various ark-known host cells (note pages 67-71, especially 69 and 70), also teach how to produce, obtain, and purifying a protein (note page 71), a radiolabeled cDNA, a oligonucleotide "consisting of at least 15 nucleotides" (note page 62, line 22) capable of hybridizing a nucleic acid, a cDNA encoding a polypeptide (note page 62), a complementary sequence to cDNA (note page 62). As for preamble "antisense" in claim 22, and the probe use to diagnose megakaryocytic abnormality in instant claim 58 are merely suggestive of an intended use and are not given patentable weight for purposes of comparing the claim with the prior art. Claims 22, and 58 read on the nucleic acid *per se.*

Claims 1, 3-12, 15-17, 19-26, and 58 are rejected under 35 U.S.C. 102(**b**) as being anticipated by Chen and Antonarakis (1997, Cytogenetics and Cell Genetics, vol. 78, pages 213-215).

Claims 1, 3-12, 15-17, 19-26, and 58 are interpreted as drawn to genomic DNA of the entire SH3DA1 gene in YAC (note the claim limitations in claim 4 and claim 26), a SH3DA1 exon with a labeled with a marker capable of being detected using fluorescence, and primers capable of hybridizing to SH3DA1 gene.

Chen and Antonarakis especially at Fig. 1 (B) teach two YAC clones of 838C7 and 860G11 between markers of D21S319 and D21S65, and these two YAC clones appear to contain the entire SH3D1A gene plus some other genes between markers of D21S319 and D21S65 of human chromosome 21q22.1 to q22.2.

Chen and Antonarakis also teach two primers capable of specifically hybridizing to a SH3D1A exon. These primers capable of amplifying the exon form the SH3D1A gene meet the limitations of the instant claims 17, and 21-22. As stated above, the preamble "antisense" in claim 22, and the probe use to diagnose megakaryocytic abnormality in instant claim 58 are merely suggestive of an intended use and are not given patentable weight for purposes of comparing the claim with the prior art. The claim read on the nucleic acid *per se*. As for claims 15-17, 19, and 20, the eletrophoretogram of the 120-pb exon as shown in Fig. 1 (A) is attached with a "a fluorophor" because Voet et al., (Biochemistry, 1994, page 815 only) teach fluorescence of the ethidium cation is

used to detect a DNA band in a gel. Thus, the 120-bp DNA band in Fig. 1 (A) of Chen and Antonarakis is most likely labeled with a fluorophor, i.e. ethidium cation. The specification at page 20 lines 11-12 does not exclude ethidium cation as a "a fluorophor". "Fluorophor" appears to be made up of "fluoro", which means "fluorescence" and "phore", which means "carrying" according to Merriam-Webster Online Dictionary downloaded from url>>m-w.com. Thus, a "fluorophor" is broadly interpreted as drawn to any substance that exhibits a florescence. Therefore, the florescent 120 bp DNA band detected in the gel as shown at Fig. 1 (A) is labeled with a fluorophor.

Claim 2, limited to SEQ ID NO:1 is not rejected because SEQ ID NO:1 is a full-length cDNA with poly A tails, a modification added after transcription according to Preiss, downloaded from url>>ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=eurekah on 8/7/04.

Although the reference does not specifically teach that the nucleic acid encodes amino acid 15-102 and other specifically recited fragments listed in claims 7-12, these recited residues in protein encoded by the SH3D1A appear to be conserved regions of the protein encoded by the gene and mostly likely have same amino acids. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the nucleic acids contained in the YAC clones 838C7 and 860G11 of the prior art do not possess the same structural characteristics of the instantly claimed invention. In the absence of evidence to the contrary, the burden is on the applicant to prove that

that the claimed invention is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Misook Yu

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Examiner
Art Unit 1642